1. ABSTRACT

- **Title**

POWER: Real World Data of 1st line Panitumumab Treatment in Combination With Chemotherapy in non-Resectable Wild Type (WT) *RAS* Metastatic Colorectal Cancer (mCRC) Subjects in Austria, Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Slovenia, Romania, Russia – an Observational Ambidirectional Study

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- **Keywords**

Panitumumab, metastatic colorectal cancer, observational study, real-world data, Europe

- **Rationale and Background**

Colorectal cancer (CRC) is the second most common cancer in Europe; up to 50% of all patients with CRC eventually develop metastatic disease. Panitumumab, an antibody against human epidermal growth factor receptor (EGFR), has been shown to be effective in mCRC and was first approved in the European Union in 2007 for the indication of adults with mCRC with non-mutated *RAS* gene. It was also approved as a first-line agent in combination with FOLFOX (folinic acid/5-flourouracil/oxaliplatin) and launched in the European countries participating in this study in 2015 - 2018. This study evaluated the use of panitumumab as first-line treatment in the metastatic setting in daily clinical practice in the participating countries.

- **Research Question and Objectives**

To obtain characteristics of subjects with wild-type (WT) *RAS* nonresectable metastatic colorectal cancer (mCRC) receiving panitumumab in combination with chemotherapy as a first-line treatment, and to describe the patterns of treatment, including first- and second-line therapies.

- **Study Design**

This was a multicentre, ambidirectional (retrospective-prospective), observational study in the selected European countries.

The primary outcome measures were to describe the characteristics of subjects with WT *RAS* nonresectable mCRC receiving panitumumab in combination with chemotherapy as a first-line treatment and to collect patterns of first- and second-line treatment. Secondary outcome measures were to estimate the response to first-line treatment and to assess safety of panitumumab.

- **Setting**

The study was conducted in the following European countries: Austria (5 study centers), Bulgaria (8 study centers), Croatia (4 study centers), Czech Republic (6 study centers), Greece (8 study centers), Hungary (7 study centers), Poland (9 study centers), Romania (8 study centers), Russia (15 study centers), and Slovenia (2 study centers). Study centers were selected to include diverse treatment settings and geographical regions within each country. The study period was from 20 November 2018 (date of first subject enrolled) to 15 December 2021 (date of last subject-last visit).

- **Subjects and Study Size, Including Dropouts**

In total, 375 subjects were enrolled into the study. The Full Analysis Set (FAS) comprised 354 subjects (94.4% of enrolled subjects), 21 subjects (5.6%) were excluded from the FAS: 20 subjects (5.3%) did not receive first-line therapy at baseline, 9 subjects (2.4%) received first-line therapy but were not in the metastatic setting at baseline, and 3 subjects (0.8%) did not receive panitumumab at baseline (some subjects could fall into more than one of these categories).

The subject recruitment numbers in each country were: Austria (n=20), Bulgaria (n=56), Croatia (n=19), the Czech Republic (n=30), Greece (n=23), Hungary (n=37), Poland (n=55), Romania (n=45), Russia (n=64), and Slovenia (n=5).

- **Data Source(s) and Methods**

Retrospective data was abstracted from subjects' medical records. The prospective data collection started at the enrolment visit and data were registered monthly thereafter upon subject visits. All tests were performed in line with routine clinical practice and no additional procedures were posed by the protocol. FACT-EGFR1-18 questionnaires were completed in countries where their use was allowed per local regulations.

- **Results**

Table 1 shows demographics and baseline characteristics. Most subjects were male (n=211, 59.6%). The mean (SD) age was 61.3 (9.9) years. Most subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0 (n=158, 44.6%) or 1 (n=159, 44.9%). The primary cancer was on the left side of the colon tract in 166 subjects (46.9%), 53 (15.0%) had right-sided colon cancer and 135 (38.1%) had rectal cancer. Most subjects (n=242, 68.4%) were initially diagnosed with stage IV cancer, 64 subjects (18.1%) had stage III, 38 subjects (10.7%) had stage II, and 6 subjects (1.7%) had stage I cancer; of 4 subjects (1.1%) cancer stage at diagnosis was missing.

Subjects had terminated their prior anticancer therapy (adjuvant chemotherapy and/or bridging chemotherapy to reimbursement decision for panitumumab) due to disease progression (n=48, 13.6%), investigator decision (n=19, 5.4%), toxicity (n=23, 6.5%),

subject's decision (n=14, 4.0%), complete response (n=7, 2.0%), completed treatment course (n=114, 32.2%), or other reasons (n=62, 17.5%).

All subjects had metastatic disease as per inclusion criteria. At panitumumab initiation, metastases were most commonly (i.e. in >25% of subjects) found at the liver (n=240, 67.8%), the lung (n=91, 25.7%), and the lymph nodes (n=81, 22.9%).

All subjects received panitumumab in combination with chemotherapy in the first-line metastatic setting. Most subjects (n=256, 72.3%) received panitumumab in combination with FOLFOX, 60 (16.9%) with FOLFIRI, 36 (10.2%) with other chemotherapy regimens, one (<1%) with 5-FU, and one (<1%) subject had panitumumab in combination with an unknown chemotherapy regimen. The median (Q1, Q3) duration of exposure to panitumumab was 8.8 (5.7, 13.9) months, with a median (Q1, Q3) cumulative dose of 4507 (2666, 7314) mg.

Tumour response data (Table 2) were available for 278 subjects (78.5%); for the remaining subjects, investigators did not report any response data in the CRF. The best overall tumour response based on RECIST criteria (as available) was complete response (n=7, 2.5%), partial response (n=56, 20.1%), stable disease (n=90, 32.4%), progressive disease (n=123, 44.2%); for 2 subjects, tumor response was not assessable (0.7%); percentages are based on the number of subjects with a response assessment. The overall response rate (ORR) comprising of complete and partial remission, was 22.7%, (n=63; 95% CI: 17.9% - 28.0%). The ORR was 20.4% (n=28/166, 95% CI: 14.0% - 28.2%) for subjects with left-sided colon cancer, 22.5% (n=9/53, 95% CI: 10.8% - 38.5%) for those with right-sided colon cancer, and 25.7% (n=26/135, 95% CI: 17.6% - 35.4%) for those with rectal cancer. Tumour shrinkage was detected in 16 subjects (4.5%).

Panitumumab-related adverse events were reported for 144 subjects (40.7%); 57 (16.1%) reported maximum grade 3, 5 (1.4%) had grade 4 and none had a grade 5 (i.e. fatal) panitumumab-related adverse events. Severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Serious panitumumab-related were reported for 15 subjects (4.2%), 1 subject (0.3%) had a life threatening panitumumab-related adverse event (large bowel obstruction, grade 3), and 13 subjects (3.7%) had panitumumab-related adverse events leading to panitumumab discontinuation (3 serious, 10 non-serious). The most frequent (>10% of subjects) panitumumab-related events according to Medical Dictionary for Regulatory Activities (MedDRA) terminology were skin and subcutaneous tissue disorders (n=121, 34.2%). Panitumumab-related adverse events leading to panitumumab discontinuation were skin and subcutaneous tissue disorders (n=8, 2.3%), gastrointestinal disorders (n=3, 0.8%), general disorders and administration site conditions (n=1, 0.3%), infections and infestations (n=1, 0.3%), and metabolism and nutrition disorders (n=1, 0.3%). Table 3 shows safety findings.

Prophylactic and/or reactive skin toxicity treatment (was reported for 143 subjects (40.4%). The most frequent treatments (>10% of subjects) were antiinfectives for systemic use, ie. systemic antibiotics, (n=111, 31.4%), and dermatologicals, i.e. topical skin treatment, (n=43, 12.1%).

Sensitivity analyses were conducted using the per protocol (PP) analysis set (n=142; 37.9% of 375 enrolled subjects), which excluded 212 subjects (56.5%) due to data collection outside the protocol window (n=156, 41.6%), data collection outside the consent window (n=137, 36.5%), first infusion of panitumumab within the 28 day time window before enrolment (n=41, 10.9%), violation of consent criteria (n=4, 1.1%), and

violation of tumour assessment criteria (n=2, 0.5%). The findings with respect to the primary and secondary outcome measures did not change using the PP analysis set as compared to the FAS.

- **Discussion**

This study describes panitumumab use and treatment patterns in the real-world setting in mostly Central and Eastern European countries. Subjects were initiated on panitumumab shortly after the drug received reimbursement and were followed for a period of up to 15 months. Subjects with nonresectable WT *RAS* mCRC were enrolled, who received panitumumab plus chemotherapy as the first line of treatment in the metastatic setting. The most frequently used chemotherapy regimen was FOLFOX (72.3%). The subjects receiving panitumumab plus chemotherapy in the first-line metastatic setting were comparatively young (at a mean age of 61.3 years) and primarily fit (with an ECOG performance status of 0 or 1). Most colorectal cancers are diagnosed at the age of 65 years or older (Siegel et al, 2020). However, at diagnosis, most subjects (68.4%) already had metastatic disease.

After a median of 8.8 months of treatment, an overall tumor response (i.e. complete plus partial response) rate of 22.7% was achieved among patients with tumor response data available. This overall tumor response is considerably lower than what was found in phase 3 studies in the first-line metastatic setting (Peeters et al, 2018), although it needs to be noted that subject populations were different. However, the present study found a higher overall response rate compared to previous observational studies conducted in the Central and Eastern European region, with 10.4% in VECTIS (Amgen Protocol Number 20080618) (Lakomy et al, 2015) and 16.0% in Amgen study number 20120271 (unpublished data). Of note, populations in these studies were different to the present study. VECTIS enrolled subjects with (Kirsten) rat sarcoma viral oncogene homolog ([*K*]*RAS*) exon 2 WT, chemorefractory mCRC receiving panitumumab monotherapy (Lakomy et al, 2015). Study 20120271 observed patients, who had been treated with panitumumab in combination with FOLFOX in the first line metastatic setting or with panitumumab combined with FOLFIRI in the second metastatic line following fluoropyrimidine-based chemotherapy (Hebart et al, 2019). Real-life data from mostly Western European cohorts showed higher overall response rates of 51.7% (study 20120271 pooled with the corresponding German and French cohorts of study 20120100) (Hebart et al, 2019). The population investigated in the present study included a large number of subjects with very advanced disease stage at initial diagnosis with 68.4% diagnosed at stage IV and 18.1% diagnosed at stage III, while commonly approximately 20% of patients have metastatic disease at initial diagnosis (Qiu et al, 2015). Major organs were affected with metastatic disease already at diagnosis with 67.8% of subjects having liver lesions, 25.7% having lesions in the lung, and 22.9% showing lesions in the lymph nodes. Taken together, these characteristics are known to negatively impact survival and treatment outcomes (Qiu et al, 2015). Additionally, the five-year survival of colorectal cancer patients diagnosed in countries of Eastern Europe is known to be lower than in Western Europe. National differences can in part be explained by differing levels of healthcare expenditure and the resulting quality of screening, diagnosis, and treatment (European Cancer Information System, 2021).

The present study recruited subjects at a time when panitumumab was newly reimbursed in the participating countries. The findings suggest that when this new treatment became available in a region that did not have a broad spectrum of available treatments reimbursed (with the exception of Austria, which contributed 20 subjects), these subjects were offered a therapy based on the evaluation of a predictive biomarker

(*RAS*) as an attempt to ensure best response to therapy and higher chances for subsequeant surgery. Future studies are required to show the characteristics of patients using panitumumab in a more mature reimbursement setting where panitumumab use has become standard beyond very late stage patients most in need.

- **Marketing Authorization Holder(s)**

Amgen Europe B.V.

- **Names and Affiliations of Principal Investigators**

Not applicable.